Periodontitis and Diabetes Mellitus

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Mayyada Al-Aysa & Olga Majeva

Supervisor: Associate Professor, dr. odont. Anne Merete Aass

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1.0 Introduction

Diabetes Mellitus (DM) is a group metabolic disorder marked by high levels of blood glucose resulting from defects in insulin production, insulin action or both. Prevalence of diabetes can vary widely depending on geography, age, sex and race.

The incidence and prevalence of DM are increasing, with more than 135 million people affected worldwide. Despite greater knowledge of the disease, one-third of people with the disease are estimated undiagnosed **(Moore et al. 2003).**

In Norway about 250.000 persons are probably affected with DM. About 25.000 individuals have the diagnosis of type 1 DM, while others have type 2 DM. Half of those with type 2 DM are still undiagnosed.

The incidence of type 1 DM is higher in Scandinavia than Europe and the U.S.A., with more than 30 cases/year/100,000 people **(Karvonen et al. 1993).** The prevalence of DM in adults is slightly higher in women than men and increases significantly with age and weight.

As the incidence of DM is increasing worldwide, a greater number of diabetic patients will be seen and treated by dental practitioners. Proper dental treatment of patients with diabetes requires knowledge about the disease.

The purpose of this project is to summarize the classification of diabetes mellitus, medical management, dental management of diabetics and the impact of diabetes on oral health in general. We are going to concentrate on the interrelationship between DM and periodontitis as two chronic conditions affecting each other.

We choose to write about this field (Periodontitis and Diabetes Mellitus) because of increasing incidence of DM. We are trying to learn more about it as well as to present useful information to our colleagues.

A better understanding of the interrelationship of diabetes and periodontitis provides more appropriate treatment of these patients. Dentists may detect undiagnosed cases of diabetes and refer patients to physicians for further evaluation.

2.0 Diabetes Mellitus (DM)

DM is a group of metabolic disorders manifested by abnormally high levels of glucose in the blood. The hyperglycemia is the result of a deficiency of insulin secretion or insulin resistance or a combination of these. Insulin is required for transport of glucose from the blood stream into the cells, where glucose is used for energy. Deficiency of insulin secretion or insulin resistance results in inability to transport glucose into the cells. Glucose is thus retained in the blood stream, causing hyperglycemia **(Mealey et al. 2004, Mealey & Ocampo 2007).**

2.1 Classification of Diabetes Mellitus

Type 1 DM

This form of DM is the result of autoimmune destruction of β-cell in pancreas, usually leading to total loss of insulin secretion. Type 1 DM is usually diagnosed in children and adolescents. In the absence of insulin these patients develop ketoacidosis, a life-threatening condition. Type 1 DM was previously called insulin-dependent diabetes, because type 1 patients are dependent on exogenous insulin for survival.

About 85–90% of patients with type1 diabetes can have one or more of the antibodies associated with the autoimmune destruction. However, some type 1 diabetics have no evidence of autoimmunity. This form of type 1 DM is strongly inherited and known as idiopathic DM **(Mealey & Ocampo 2007).**

In Norway about 25.000 people have the diagnosis of type 1 DM. Every year about 600 new cases are diagnosed to have type 1 DM, about 250 of them are children under 15 years of age. The number of children diagnosed to have type 1 DM is doubled during the last 30 year in Norway (http://www.diabetes.no/index.asp?id=23017).

Type 2 DM

Type 2 DM is present in 90–95% of patients with the disease. Type 2 DM is characterized by peripheral resistance of insulin. As the condition progresses, glucose production by the liver increases, and insulin secretion decreases. These changes lead to sustained hyperglycemia.

These patients can remain undiagnosed for many years because the hyperglycemia appears gradually and often without symptoms. The risk of developing this form of DM increases with age, obesity, previous history of gestational DM and lack of physical activity **(Mealey & Ocampo 2007).**

The highest prevalence of type 2 DM in the world is found in Pima Indians in the U.S.A. More than 50% of Pima Indians older than 35 years have type 2 DM. In the past 20 years, the incidence of type 2 DM is increased in children and teenagers. Increasing incidence of type 2 DM among children is associated with obesity and genetics (**Moore et al. 2003).** (http://www.apotek1.no/helsesenter/diabetes/dette_er_diabetes/diabetes_type_2_). In Norway about 225 000 persons have type 2 DM, about half of them is undiagnosed. Every year 6000-7000 get the diagnosis of type 2 DM. The number of patients with type 2 DM increased four times in the last 50 year (*http://www.diabetes.no/index.asp?id=23018*).

Gestational Diabetes Mellitus

Gestational diabetes mellitus is defined as glucose intolerance, which is first recognized during pregnancy. It only affects 1-2% of all pregnancies in Norway. Prenatal care in Norway is very well organized, and thus it probably reduces the risk of complications. (http://www.apotek1.no/helsesenter/diabetes/dette_er_diabetes/svangerskapsdiabetes)

Gestational DM usually has its onset in the third trimester of pregnancy. Women at high risk are those older than 25 years of age with positive family history of DM and obesity. The increasing demand of insulin during pregnancy and hormonal changes are predisposing these women to the development of gestational DM **(Mealey & Ocampo 2007).**

Other specific types of diabetes

- Genetic defects of the β cell.
- Genetic defects in insulin action.
- Diseases of the exocrine pancreas.
- Endocrinopathies.
- Drug- or chemical-induced diabetes.
- Infections.

- Other genetic syndromes sometimes associated with diabetes. **(Mealey & Ocampo 2007)**

Impaired glucose tolerance and impaired fasting glucose

This is a condition called pre-diabetes. These individuals are normoglycemic but demonstrate elevated blood glucose levels after fasting and after glucose load. This condition is a strong predictor for future development of type 2 DM **(Mealey & Ocampo 2007).**

2.2 Medical management of diabetes mellitus

Treatment of DM includes not only the normalization of glycemia, but interventions to prevent initiation of complications or their progression. Nonpharmacological interventions are dietary control and exercise leading to weight loss and improvement of glycemic control. Dietary control that reduces carbohydrate and lipid consumption will reduce the likelihood of developing microvascular and macrovascular complications of DM (**Robertson et al. 2003).**

Pharmacological therapy

o Insulin therapy

Insulin therapy is indicated for all patients with type 1 DM. Insulin is also used in type 2 diabetic patients with insulinopenia in whom diet and oral agents are inadequate to attain target glycemic control. Insulin therapy is also indicated for women with gestational DM who are not controlled with diet alone. Therapy is usually initiated with a single dose of long-acting insulin. Multiple split-dose regimens using rapid or short-acting insulin before meals are then added. Insulin is usually administered as a bolus dose given subcutaneously with a syringe. Insulin pump or continuous subcutaneous insulin infusion therapy is another option for intensive insulin therapy. Insulin pumps are programmed to deliver small continuous basal doses of insulin throughout the day, with bolus dosing before meals **(Mealey & Ocampo 2007).**

Side-effects of insulin include increased risk of hypoglycemia. As a practical matter, clinicians should be aware of the time of peak insulin action for each insulin preparation

because the risk for peroperative hypoglycemia is usually highest at times of peak insulin action.

- **Oral agents**

The classes of oral hypoglycemic agents reduce plasma glucose levels by one or more methods: increasing insulin secretion, reducing insulin resistance or delaying glucose absorption by the gut (**Robertson et al. 2003).**

Side-effects of oral hypoglycemic agents include weight gain and occasional hypoglycemia, although the risk of hypoglycemia varies, depending on the type of the oral hypoglycemic agent **(Mealey & Ocampo 2007).**

2.3 Glycemic control:

The best method of determining the glycemic control in a known diabetic patient is the Glycated Haemoglobin Assay. This test allows determination of blood glucose status over the 30-90 days before collection of blood sample. As glucose circulates in the blood stream, it becomes attached to a portion of the haemoglobin molecule on red blood cells. High plasma glucose over time gives a higher percentage of haemoglobin that becomes glycated. The American Diabetes Association (2003) recommends that individuals with DM should attempt to achieve a target HBA1c of less than 7%, whereas an HBA1c >8% suggests that a change in patient management may be needed to improve glycemic control (**Rees & Mealey 2004).**

2.4 Systemic complications of diabetes mellitus

Acute complications of diabetes mellitus

Diabetic ketoacidosis

Diabetic ketoacidosis is the most common life-threatening hyperglycemic emergency in patients with DM and it is the leading cause of death in children with type 1 DM **(Charfen & Fernandez-Frackelton 2005)**. Diabetic ketoacidosis is a metabolic abnormality characterized by hyperglycemia and metabolic acidosis as a result of hyperketonemia with neurological manifestations **(Kitabchi & Wall 1995)**. It is usually preceded by polyuria, polydipsia, fatigue, nausea, vomiting, and finally depression of sensorium and coma. Patients present themselves with one or more of the following: hyperventilation (Kussmaul breathing), signs of dehydration, 'fruity' breath odor of acetone, hypotension, tachycardia and hypothermia.

Management includes continuous intravenous infusion of regular (short-acting) insulin **(DeFronzo et al. 1994)**. Fluid replacement should be initiated as soon as possible to improve circulatory volume and tissue perfusion.

Hyperglycemic hyperosmolar state

Hyperglycemic hyperosmolar state is the second most common life-threatening form of decompensated DM **(Kitabchi et al. 2001)**. The greatest risk is for elderly people, particularly those bedridden or dependent on others for their daily care. Infection is a common precipitating event, as is poor compliance with insulin therapy. Hyperglycemic hyperosmolar state is a metabolic abnormality characterized by severe hyperglycemia in the absence of significant ketosis, with hyperosmolarity and dehydration secondary to insulin deficiency, and massive glycosuria leading to excessive water loss **(Ennis et al. 1994)**. Treatment of hyperglycemic hyperosmolar state consists of hydration, electrolyte replacement and small amounts of insulin.

Hypoglycemia

Hypoglycemia is the result of excess insulin in the blood, which causes excessively low blood sugar levels. While symptoms vary from person to person and range in severity, there are a few common complaints when the blood sugar is too low. The symptoms are caused by the nervous system's response to low levels of circulating blood sugar. The symptoms usually occur gradually and may be associated with a rapid heart beat, perspiration, shakiness and anxiety (some of the warning signs). If these signs are ignored, and blood sugar levels continue to fall, more severe symptoms may occur, such as confusion, behaviour changes and unconsciousness. These later symptoms are the result of a reduction in fuel source to the brain. Eventually, a patient can develop a seizure and coma may ensure.

Chronic macrovascular complications of diabetes mellitus

Cardiovascular disease

The risk of cardiovascular disease is markedly increased in patients with DM, and it is the major cause of mortality for these individuals. Several risk factors are associated with higher prevalence of cardiovascular disease in type 2 DM: abdominal obesity, insulin resistance, hypertension and dyslipidemia **(Sorrentino 2005)**. The prevention or slowing of cardiovascular disease is achieved with the intervention of cardiovascular risk factors; these include blood pressure control, dyslipidemia treatment, smoking cessation and aspirin therapy. Importantly, improved glycemic control has been shown to reduce the risk of cardiovascular events **(Mealey & Ocampo 2007)**.

Chronic microvascular complications of diabetes mellitus

Nephropathy

Diabetic nephropathy occurs in 20–40% of patients with DM and is the leading cause of end-stage renal disease **(Mealey & Ocampo 2007)**. The earliest clinical evidence of nephropathy is the appearance of low but abnormal levels (30 mg/day or 20 μg/min) of albumin in the urine **(Gross et al. 2005)**. With progression of the disease, large amounts of protein excreted in the urine (proteinuria) and renal hypertension, may then progress to end-stage renal disease.

Retinopathy

Diabetic retinopathy is characterized by vascular closure, and proliferative diabetic retinopathy, characterized by the growth of new blood vessels on the retina and posterior surface of the vitreous **(Bloomgarden 2004)**. Glycemic control and blood pressure control can prevent and delay the progression of diabetic retinopathy in patients with diabetes (**Higgins et al. 2007).**

Neuropathy

Neuropathy is a common complication of both type 1 and type 2 DM, with predominantly small-fiber involvement beginning at the distal extremities and progressively becoming more proximal with time and duration of DM. ‘Burning’ or ‘prickly’ feet are common descriptions from diabetic neuropathy patients. Recognition of neuropathy is very important because it represents an independent risk factor for ulcers of the skin and amputations. Diabetic neuropathy causes loss of protective sensation and alteration of biomechanics, which are associated with the increased risk of limb amputation **(Kelkar 2005).**

2.5 Oral complications of diabetes mellitus.

Periodontal diseases

DM is considered as a risk factor for development of periodontal disease. The glycemic control is an important factor which affects the prevalence and severity of periodontal disease. The duration of DM appears to affect the severity of periodontal disease.

Several factors have been proposed to explain the increased susceptibility to periodontal diseases in diabetics, including alteration in subgingival microflora, alteration in host response and altered wound healing **(Ryan et al. 2003).**

Salivary dysfunction & xerostomia

Patients with uncontrolled diabetes are susceptible to salivary disorders. Reduced salivary flow rate may be due to dehydration caused by polyurea or to alterations in the basement membrane of salivary glands. In addition people with DM often take medication not only for DM but for other related systemic conditions. These medications may have significant xerostomic effect (**Vernillo 2003).**

Dental caries

An increase in the rate of dental caries may be related to salivary dysfunction. In addition patients with hyperglycemia present high glucose levels in gingival crevicular fluid (GCF) which could increase their risk of developing new and recurrent dental caries. Regular dental visits and caries prevention programs with fluoride supplement is important for these patients (**Vernillo 2003, Nauntofte et al. 2003).**

Figure 1. Salivary hypofunction, xerostomia and dental caries in diabetic patient (Ship 2003).

Oral mucosal diseases.

DM is associated with a greater likelihood of developing certain oral mucosal disorders. There are reports of greater prevalence of lichen planus, recurrent aphthous stomatitis, and oral fungal infections. While these associations have not been found consistently in all populations of subjects with DM**,** they may be due to alterations in immune responsiveness **(Ship 2003).**

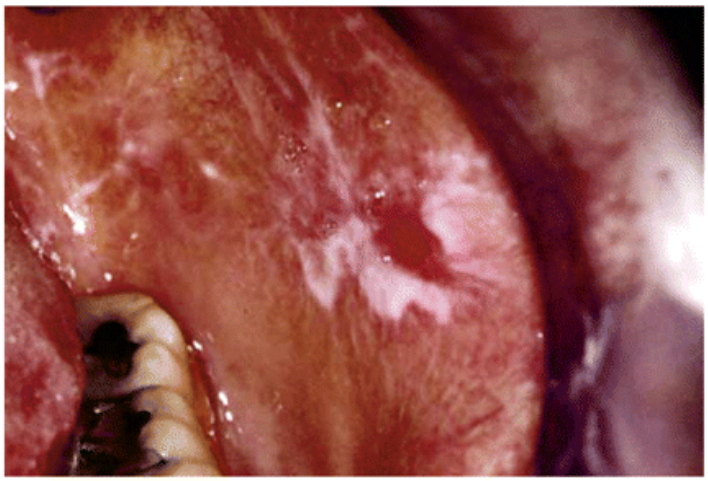


Figure 2. Oral reticular lichen planus in a patient with type 2 diabetes (Ship 2003).

Candidiasis

Another manifestation of DM and an oral sign of systemic immunosuppression is the presence of opportunistic infections, such as oral candidiasis. Several factors like poor glycemic control, xerostomia and wearing dentures, are associated with the development of candidiasis in diabetic patients. This may be superimposed with cigarette smoking and insufficient oral hygiene. The oral health care professional can readily make the diagnosis of oral candidiasis and provide therapy. Most importantly, the dentist should pursue the infection's aetiology. This may help in the detection of undiagnosed patients with DM **(Ship 2003).**

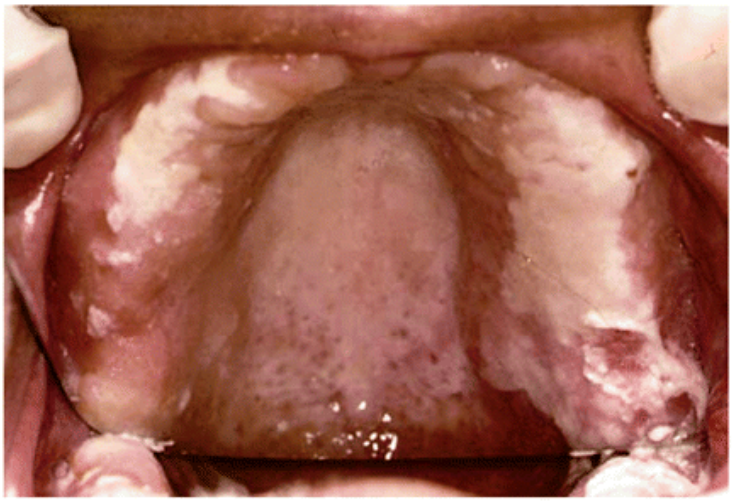


Figure 3. Oral pseudomembraneous candidiasis in a patient with poorly controlled type 1 diabetes (Ship 2003).

Burning mouth syndrome

Patients with burning mouth or burning tongue syndrome usually exhibit no clinically detectable lesions, although the symptoms of pain and burning can be intense. Etiologic factors can include salivary dysfunction, candidiasis and neuropathy of autonomic and sensory nerves in the oral cavity. The prevalence of neuropathy is increasing with the progression of DM. Neuropathy may lead to oral symptoms of paresthesia and tingling, numbness, burning or pain caused by pathological changes involving the nerves in the oral region **(Vernillo 2003).**

3.0 Periodontal diseases

Periodontal disease is a multifactorial disease that has been associated with multiple risk factors. These disorders are triggered by the accumulation of dental plaque. The clinical signs are caused by the resultant inflammatory and immune responses. There are two main diagnostic categories of periodontal diseases, Gingivitis and Periodontitis.
Gingivitis is the presence of gingival inflammation which results in reversible destruction of the gingival tissues. Gingivitis is characterized by gingival redness, oedema, bleeding, changes in contour, loss of tissue adaptation to the teeth, and increased flow of GCF.

Periodontitis is the presence of inflammation at sites where there has been apical migration of the junctional epithelium onto the root surface with concomitant loss of connective tissue and alveolar bone.
Clinically, periodontitis is usually characterised by pocket formation, loss of clinical attachment and bleeding on probing (BOP). Suppuration and increased mobility of the tooth may also be present. Radiographically it is characterised by horizontal and/or vertical bone loss.
Periodontitis is a multifactorial disease; several risk factors are associated with the development of periodontitis:

- Microbial risk factor: More than 500 species have been isolated from periodontal pockets. It is likely that only a small percentage of these bacteria are periodontal pathogens. *Aggregatibacter actinomycetemcomitans, Porphyromonas gingivalis,*

Prevotella intermedia, Tannerella forsythia, Fusobacterium nucleatum and Peptostreptococcus micros are all significant markers for destructive periodontal disease in adult subjects. Based on calculated odds ratios, *T. forsythia* and *P. gingivalis* are the strongest bacterial markers for this disease and are infrequently cultured from subjects without periodontal bone loss (**Van Winkelhoff et al. 2002)**.

- Systemic risk factors**:** Certain systemic diseases may impair host defence to periodontal infection e.g., DM, HIV and cyclic neutropenia.
- Genetic risk factor, gender and ethnicity.
- Environmental risk factors: Oral hygiene, cigarette smoking, stress and oral hygiene.
- Local risk factors: These factors likely act by promoting plaque accumulation e.g., anatomical, restorative, orthodontic and habits contributing factors (**Greenwell et al. 2004, Lamster 2006).**

Epidemiology

Epidemiological studies of periodontitis show that most adults have mild to moderate periodontitis. A smaller group of adults have aggressive and more advanced periodontitis (**Löe et al 1986).**

Epidemiological studies from Europe show that few individuals less than 30 years of age have advanced or aggressive periodontitis. The prevalence of advanced/aggressive periodontitis is increasing with age, about 10-15% of adult population. In Norway it was reported that 13% of individuals 45-54 years of age had one or several periodontal pockets of 6 mm or more (**Aleksejuniene & Holst 2004).**

3.1 Classification of periodontal disease

The currently accepted classification system was described in 1999. It is based on an infection/host paradigm. It follows the concept that plaque- induced periodontal diseases are infections occurring as a result of host inflammatory and immunologic responses to dental plaque bacteria (Workshop on the Classification of Periodontal Diseases 1999).

1. Gingival diseases.
   - Dental plaque –induced gingival Diseases.
   - Nonplaque-induced gingival lesions.

2. Chronic periodontitis.
    - Localized
    - Generalized
3. Aggressive periodontitis.
    - Localized
    - Generalized
4. Periodontitis as a manifestation of Systemic Diseases.
5. Necrotizing periodontal diseases.
6. Abscesses of the periodontium.
7. Periodontitis associated with endodontic lesions.
8. Developmental or acquired deformities and conditions.

The diagnostic system used at the Dental faculty in the Oslo is based on three main classifications:

A: Localization.

B: Severity.

C: Patient's age.

Classification according to localization:

1- Localized (1-7 teeth)
2- Generalized (> 7 teeth)

Classification according to severity:

1- Mild: Not diagnosed as moderate or severe periodontitis.
2- Moderate: at least 2 teeth with bone loss >1/3, but < ½ of radiographic root length or clinical attachment loss >3 mm, but <5 mm.
3- Severe: at least 2 teeth with bone loss >1/2 of radiographic root length or clinical attachment loss > 5 mm.

Classification according to patient's age:

1- young < 30 year
2- adult >30 year

3.2 Pathogenesis

Periodontal disease is initiated by the accumulation of microbial plaque on the tooth surface. The sulcular epithelial cells will come in contact with microbial enzymes, waste product and surface component of bacteria. The epithelial and dendritic cells are triggered by microbial substances to produce pro-inflammatory cytokines and other chemical mediators. These mediators induce an inflammatory response within the gingival tissue. Thus the gingiva becomes oedematous due to fluid accumulation and cell infiltration.

Polymorphonuclear cells (PMNs) along with other leukocytes such as monocyte, macrophages, and lymphocytes are attracted to the gingival tissue by the chemotactic factors including microbial proteins and host factors such as the cytokine Interleukin-8 (IL-8) . The PMNs arrive in the gingival crevice and begin their function of phagocytising the bacteria. The macrophages have a useful function in the gingival crevice by phagocytising the dead PMNs and their harmful enzymes. This is called the scavenging function of macrophages which is useful in damping down the inflammation.

The immune response begins when Langerhans cells within the gingival tissue phagocyte bacterial antigens and take it to the regional lymph nodes. In the lymph node the Langerhans cells present the bacterial antigen to the lymphocytes. Committed lymphocytes return to site of bacterial exposure (gingival tissue) where B cells transform to plasma cells which produce antibody, or T cells differentiate to produce cell mediated immune response. These antibodies will aid the PMNs in the phagocytises of bacterial pathogens in the gingival crevice.

The inflammatory cell infiltrate in the gingiva needs space to begin its function. Therefore the structural components like fibroblasts and collagen must be lost to create physical room for the infiltrating leukocytes. These inflammatory cells will produce matrix degrading enzymes (MMP-8) leading to connective tissue destruction. Furthermore as the layers of junctional epithelium are broken down and the contact to the tooth is lost, the periodontal pocket is formed. The anaerobic environment in the periodontal pocket will invite the colonization of the facultative and anaerobic microorganisms.

As the infiltrate extend apically, the bone is resorbed to make more room for the defence cells. The production of Interlukin 1β (IL-1β), Tumor Necrosis Factor α (TNFα), and Prostoglandin 2 (PGE_2) will increase in response to bacterial infection and lead to bone resorption.
When the disease in untreated, the tissue destruction caused by the inflammatory response overwhelms any tissue repair and may end with deepening of the periodontal pocket, attachment loss, bone resorption, granulation tissue formation and tooth loss.
(Kinane et al. 2003, Nisengard et al. 2006).

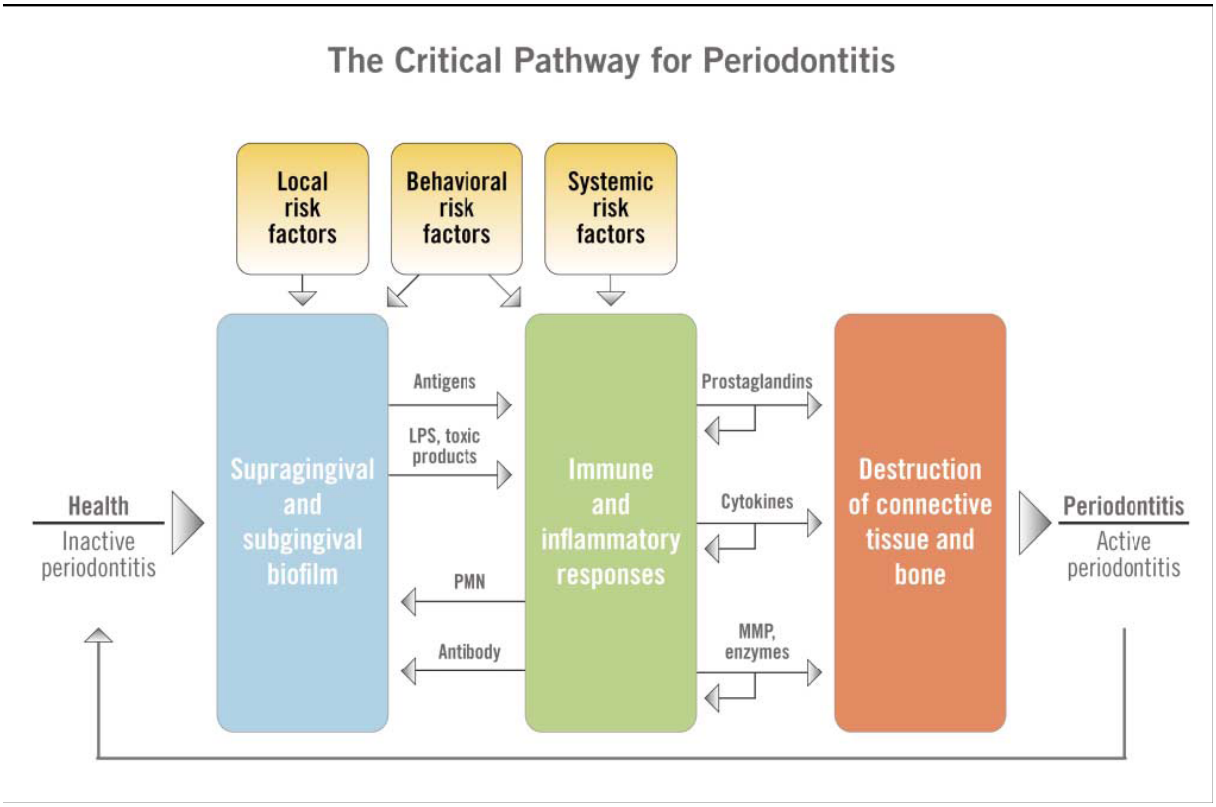


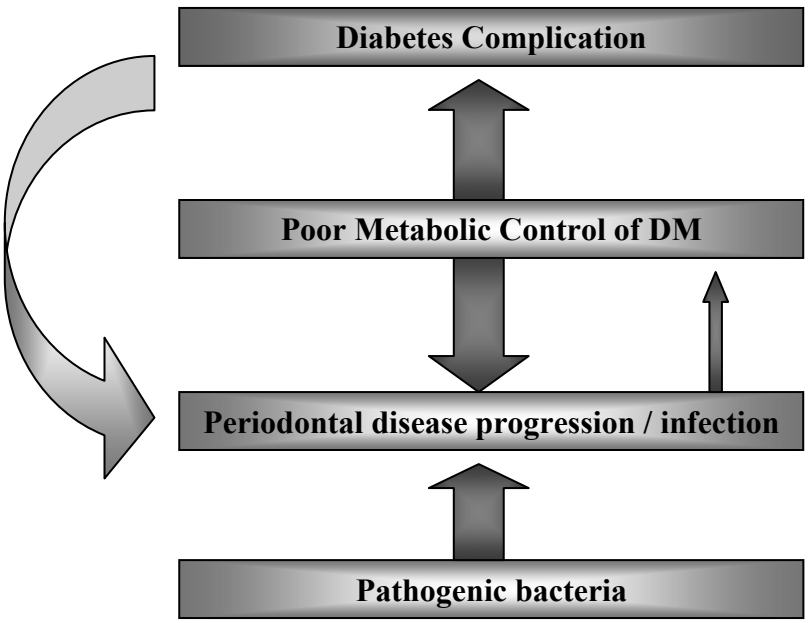
Figure 4. The critical pathway of periodontitis (Lamster 2006).

4.0 Association between Periodontitis and Diabetes mellitus

There is a general agreement that DM is a risk factor for periodontitis. Diabetics have a significant higher prevalence of periodontitis compared to non-diabetics **(Papapanou 1996).** The severity of periodontitis was significantly higher in diabetic patients compared to non-diabetic patients **(Khader et al. 2006).**

Glycemic control is considered as the risk factor for the development of periodontitis in diabetic patients. Poorly controlled diabetics had three fold increases in risk of having periodontitis compared to non-diabetics. Conversely, well controlled diabetics had no significant increase of periodontitis **(Tsai et al. 2002).** Some studies show that poorly controlled diabetes increases the risk of progressive bone loss and attachment loss over time **(Taylor et al. 1998)**.

The duration of having diabetes is an important factor to evaluate the risk of DM on the development of periodontitis **(Ryan et al. 2003).**



Figur 5. Diabetes control and periodontal disease progression (Palmer & Soory 2003).

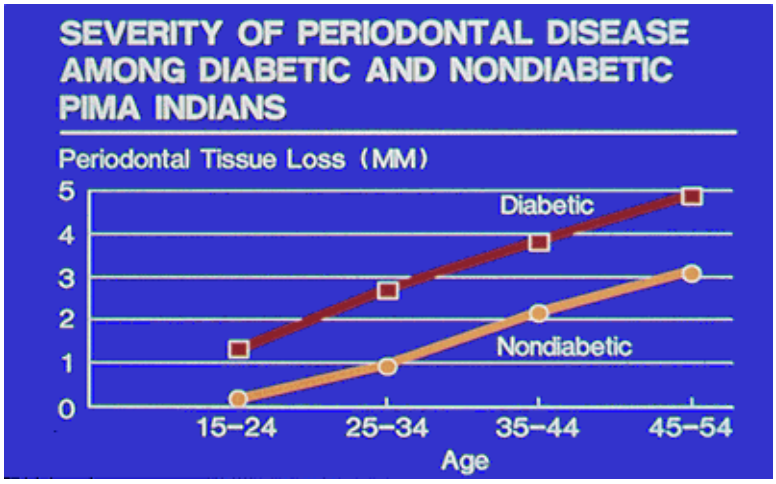
A meta-analysis of data from a number of studies demonstrates a statistically significant association between type 1 DM and periodontal disease. Some studies showed more pronounced gingivitis in type 1 DM, but failed to detect notable differences in periodontal conditions between type 1 diabetics and healthy subjects **(Papapanou 1996).** The severity of periodontal disease was shown to increase with the severity of organ complications and the duration of DM. Type 1 diabetic patients with advanced complications had significantly more bleeding on probing, pockets ≥ 4 mm deep, and had more attachment loss than patients without complications (**Karjalainen et al. 1994).**

Periodontal destruction can start very early in life in diabetic children and becomes more prominent as children become adolescents (**Lalla et al. 2006).**

Many studies on periodontal disease in patients with type 2 DM have been conducted in the Pima Indians in the U.S.A. This population has the highest prevalence of DM in the world, with 50% of its population older than 35 years of age being diagnosed with type 2 DM.

The diabetics in the Pima Indians population had higher prevalence and severity of periodontitis compared to non-diabetics of the same population. It was concluded that DM increases the risk of developing periodontitis by about three fold (**Shlossman et al. 1990).**

Type 2 DM may also increase the risk of alveolar bone destruction over time. In a two-year longitudinal study was reported a fourfold increased risk of progressive alveolar bone loss in adults with type 2 diabetics compared with non-diabetics **(Taylor et al. 1998)**.



Figur 6. The severity of periodontal disease among diabetic and nondiabetic Pima Indians (http://www.diabetesmonitor.com/b285.htm).

4.1.0 Effect of diabetes on the periodontium

4.1.1 Effect on microflora

Several studies have focused on the alteration of oral microflora in diabetics. Some of these studies have found a relation between glycemic control and alterations in microflora which may increase the susceptibility of diabetics to periodontal disease. **Ciantar et al**. (2005) has found that the counts of Capnocytophaga species were significantly higher in periodontal pockets of diabetics compared to periodontal pockets in healthy individuals.

Other studies did not find a significant difference in the oral microflora between diabetics and healthy individuals. **Thorstenseon et al**. (1996) studied several bacterial species in the subgingival microflora in long-term type 1 diabetics and non-diabetics. They reported that *A. actinomycetumcomitans, C. rectus, Capnocytophaga species, E. corrodens, F. nucleatum, P. gingivalis, and P. intermedia* are recovered in diabetics a well as non-diabetics. The same study observed that *P. gingivalis* was detected both in shallow and deep pockets in diabetic subjects, whereas the pathogen was only found in deep pockets in non-diabetic individuals. Local environmental changes in diabetics because of salivary alteration and high glucose levels in GCF may result in shifts of the microbial flora **(Andersen et al. 2007).**

The differences of the results of these studies suggest that alterations in the host response to existing periodontal pathogens may primarily be responsible for the more aggressive periodontal destruction observed in diabetics (**Ryan et al. 2003).**

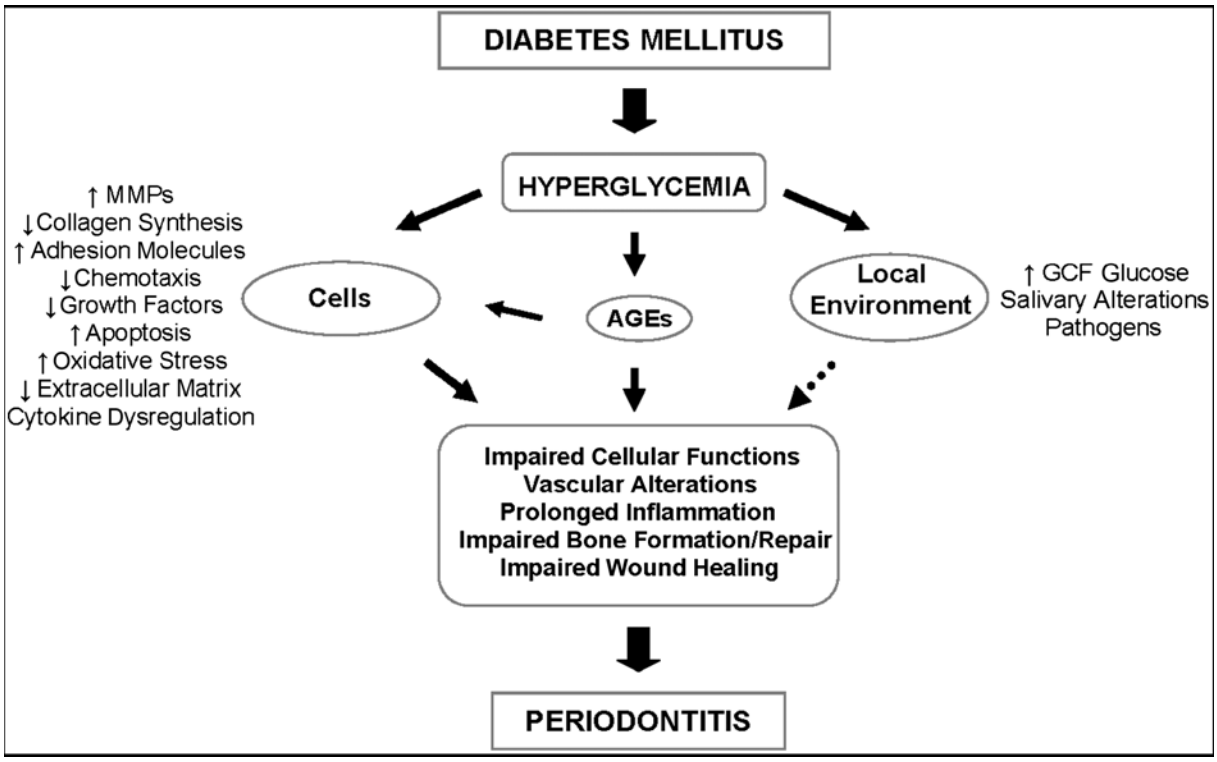


Figure 7. Mechanisms explaining the increased susceptibility to periodontitis in diabetics (Andersen et al. 2007).

4.1.2 Advanced Glycation End Products (AGEs)

The sustained hyperglycemia in poorly controlled diabetics in combination with elevations of serum low density lipoproteins and triglycerides will induce an irreversible glycation of proteins like collagen and lipids to form the AGEs.
AGEs will accumulate in tissues of diabetic patients and are thought to be a major link between the various diabetic complications. They may also be involved in tissue changes within the periodontium. Therefore, poorly controlled diabetics show higher AGEs levels and are more susceptible to periodontitis. The biologic effect of AGEs is mediated by the receptor for AGEs (RAGE) which is found on the surface of smooth muscle cells, endothelial cells, neurons, monocytes and macrophages **(Lalla et al. 2001).**

AGEs and blood vessels

Hyperglycemia results in increased expression of RAGE and increased interactions between the AGE and RAGE on endothelial cells, causing precoagulatory changes, thrombus formation and thickening of basement membrane of microvasculature (microangiopathy). Microangipathy is reported in gingival tissues from diabetic rodents and poorly controlled diabetics (**Seppala et al. 1997, Gul & Ozsoy 2003).**
Microangiopathy results in impaired exchange of cells, oxygen, and metabolic products between the intra- and the extracellular compartment, ultimately affecting host response and tissue repair.

4.1.3 Effect on host response

Polymorphoneuclear Leucocytes (PMNs)

PMNs act as first-line-of-defence cells and the reduction of their function may explain the high susceptibility of diabetics to infection. Clinical investigations in diabetic patients and experimental studies in diabetic rats and mice have clearly demonstrated that the defects of PMNs include chemotactic, phagocytic and bactericidal activities. This defective PMNs function is highly related to poor glycemic control (**Alba-Loureiro et al. 2007).**
GCF collagenase concentration is higher in diabetics and it is primarily derived from PMNs. (**Sorsa et al. 1992).**

Monocytes, macrophages and cytokines

Higher concentration of cytokines (IL-1β, PGE_2, TNF-α) has been detected in GCF of diabetic patients with periodontitis compared to non-diabetic patients. The release of these cytokines in response to bacterial lipopolysaccharides (LPS) by monocytes was significantly higher in diabetics than in non-diabetics. This hyperinflammatory response is thought to be a result of AGE-RAGE interaction on monocytes and macrophages. This can result in the formation of a destructive cell phenotype with increased sensitivity to stimuli, resulting in excessive release of cytokines **(Salvi et al. 1998)**. AGE-RAGE binding on macrophage surfaces may alter macrophage phenotype. This may be responsible for dysregulation of macrophages cytokine production and increased inflammatory tissue destruction and alveolar bone loss. It may alter the scavenging function of macrophages and delay the wound healing **(Iacopino 1995).**

4.1.4 Effect on collagen metabolism

Collagen is the major structural protein in the periodontium and it is synthesized by gingival fibroblasts.

Collagen synthesis is reduced in diabetic patients compared to non-diabetics. The formation of AGE in the gingival tissue may alter the cellular function in gingival tissue due to oxidative stress **(Schmidt et al. 1996).** Gingival fibroblasts produce decreased amount of collagen and glycosaminoglycans in hyperglycemic conditions.

Elevated collagenase levels in gingival tissues of diabetics will increase the degradation of collagen in the periodontium. Therefore the homeostasis between tissue destruction and tissue formation is altered in diabetics. The increase in tissue destruction by collagenases and the decrease in collagen formation by fibroblasts will lead to more tissue destruction and progression of periodontitis.

AGE formation on collagen results in increasing the cross-linking between collagen molecules and decreasing its solubility. The result of these changes in collagen metabolism is an alteration in normal homeostatic collagen turnover **(Mealey & Oates 2006).**

4.1.5 Effect on wound healing and treatment response

Several factors are thought to be responsible for the altered wound healing in diabetics.

- Gingival microangiopathy due to thickening of the capillary basement membrane in the hyperglycaemic environment can impair oxygen diffusion, metabolic waste elimination, PMN migration and diffusion of antibodies.
- Reduction of collagen synthesis by fibroblasts.
- Increased collagen degradation due to increased collagenase activity in diabetics.
- Glycolysation of existing collagen at wound margins.
- Defective remodelling and rapid degradation of newly synthesized, poorly cross-linked collagen.

(Palmer & Soory 2003)

The mitogenic activity of platelets in diabetics has been found to be decreased. These defective platelets have diminished ability to induce fibroblast proliferation than did platelets of non-diabetics. This may be associated with altered wound healing in diabetics **(Caenazzo et al. 1991).**

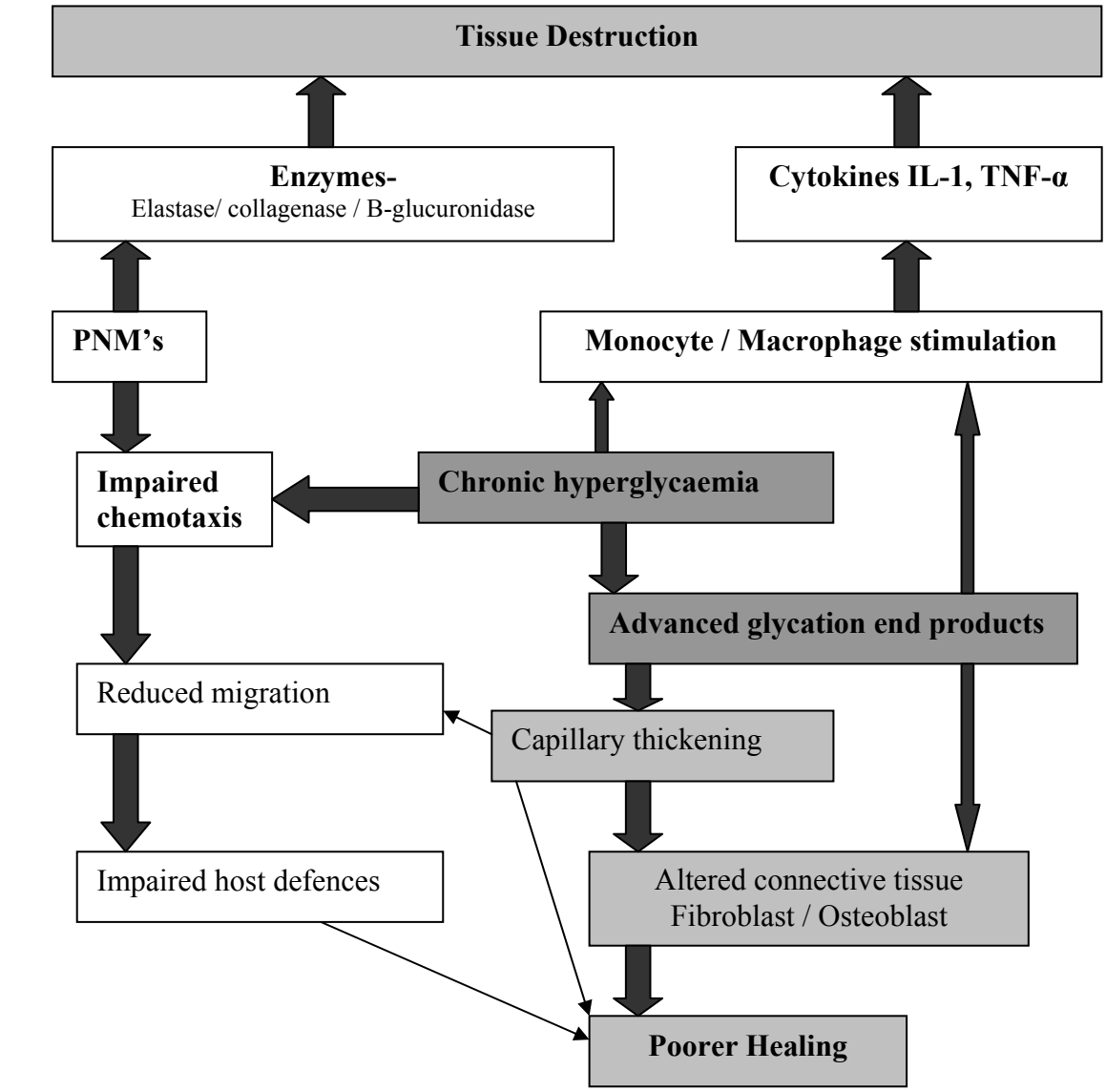


Figure 8. Effect of Diabetes mellitus on the host response (Palmer & Soory 2003).

4.2 Influence of periodontitis on diabetic status

The inflammatory nature of periodontitis may alter the glycemic control in a similar manner to obesity and other inflammatory conditions. Studies have shown that diabetic patients with periodontal infection have a greater risk of worsening glycemic control over time compared to diabetic subjects without periodontitis (**Taylor et al. 1996**). Some studies suggest that periodontal disease may be a significant risk factor for myocardial infarction and stroke in diabetics. A recent longitudinal trial examined the effect of periodontal disease on mortality from multiple causes in over 600 subjects with type 2 DM in the Pima Indians population (**Saremi et al. 2005**). In subjects with severe periodontitis, the death rate from ischemic heart disease was 2.3 times higher than the rate in subjects with no periodontitis or only slight disease, when adjusted for other known risk factors. The death rate from diabetic nephropathy was 8.5 times higher in those subjects with severe periodontitis. The overall mortality rate from cardio-renal disease was 3.5-fold higher in subjects with severe periodontitis, suggesting that the presence of periodontal disease poses a risk for cardiovascular and renal mortality in people with diabetes.

The following biologic mechanisms have been proposed to explain how periodontitis may affect the systemic environment: entrance of bacteria or bacterial products, such as LPSs, from the ulcerated periodontal pocket into the systemic circulation and/or systemic effects of inflammatory mediators like TNF-α, IL-1β, and IL-6 produced locally in response to periodontal infection. These mediators potentially can increase low-grade inflammation and worsen insulin resistance **(Li et al. 2000, Grossi 2001).**

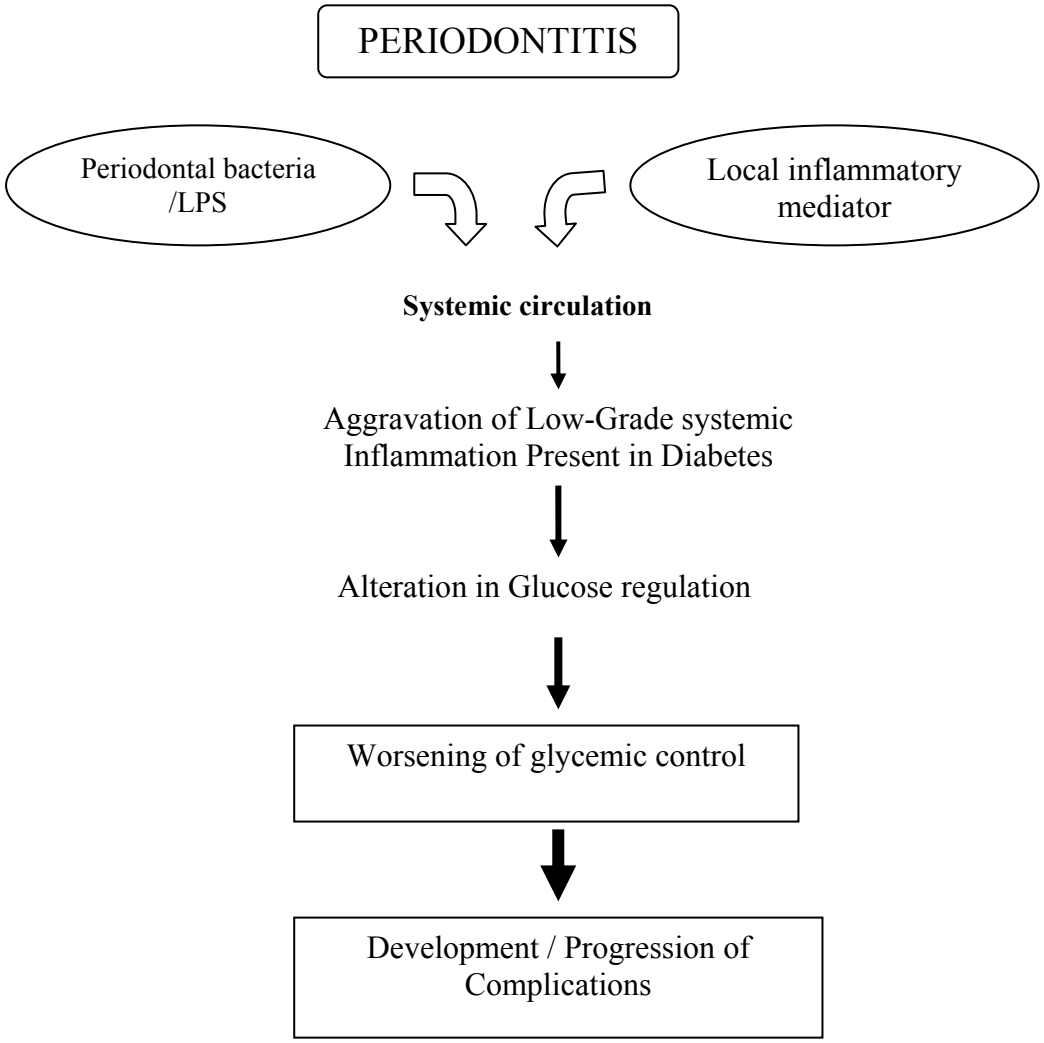


Figure 9. Potential mechanisms for the influence of periodontitis on the diabetic status (Andersen et al. 2007).

Many mechanisms may account for the metabolic effect of TNF-α, including downregulation of genes related to normal insulin action and direct effects on insulin signalling, glucose transport, and pancreatic β cells **(Grimble 2002).**
IL-6 was reported to modulate production of TNF-α and has been associated with insulin resistance; IL-1β in turn, seems to participate in the regulation of glucose uptake **(Fernandez-Real & Ricart 2003).**

Thus, these mediators have detrimental effects on glucose metabolism. Patients with diabetes and periodontitis have enhanced production of inflammatory mediators in the gingival tissues compared to non-diabetics **(Salvi et al. 1998).**
In support of this observation, periodontitis superimposed on diabetes in rats resulted in enhanced IL-1β in fat tissue and impaired glucose tolerance (**Andersen et al 2006).**
In contrast, some human and rodent studies did not find alterations in cytokine expression when periodontitis was superimposed on diabetics **(Takeda et al. 2006).**

5.0 Periodontal treatment and glycemic control

The periodontal treatment of diabetic patients depends on glycemic control. In general, patients with well-controlled type 1 or type 2 diabetes may have no more significant risk of experiencing oral disease progression than do those without diabetes and hence, can be treated similarly.

The response to therapy may not be as favourable in patients with poor glycemic control (HBA1c >10%) as it is in those with better control (HBA1c <8%). In poorly controlled diabetic patients, the dentist should provide proper periodontal treatment. If an infection is associated with systemic signs or symptoms such as increased temperature or lymphadenopathy, a systemic antibiotic treatment also may be indicated. A systemic antibiotic treatment such as Doxycyclin (100 mg/day for 14 days), used in combination with scaling and root planning, may help improve the glycemic control **(Grossi 2001, Rees & Mealey 2004).**

Only when glycemic control has improved, should further periodontal therapy such as surgical care, be considered. Otherwise, the response to the treatment may be less favourable **(Rees & Mealey 2004).**

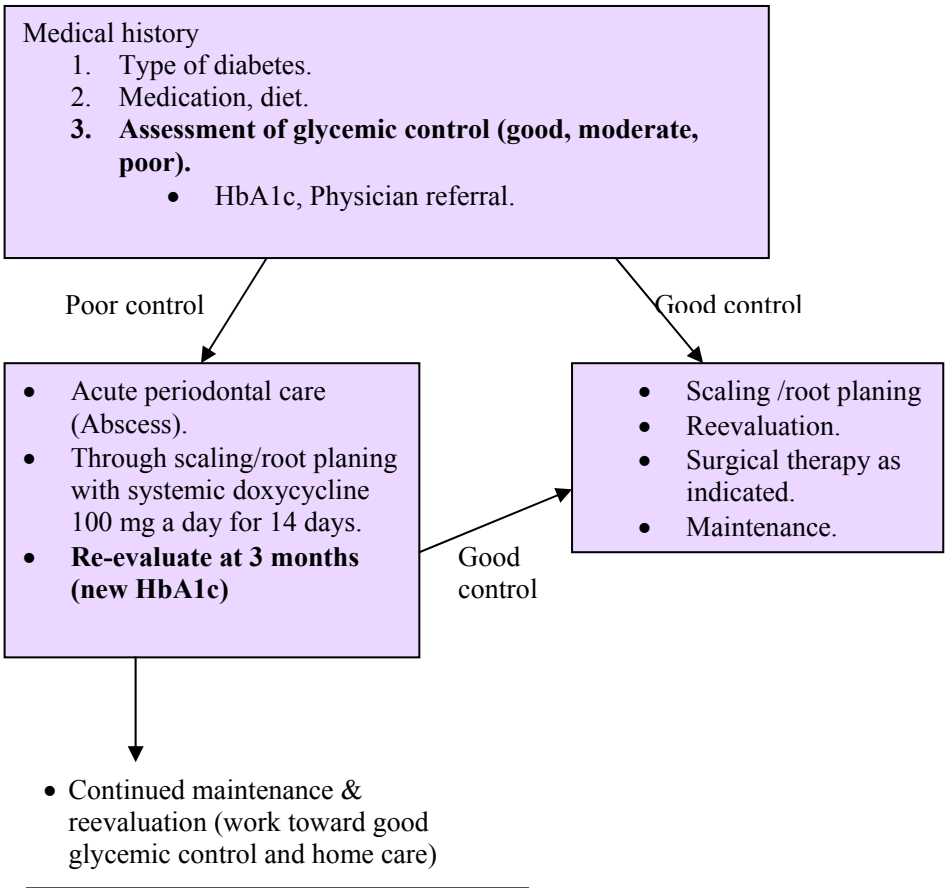


Figure 10. Pathway of periodontal therapy for patients with diabetes (Rees & Mealey 2004).

A meta-analysis of 10 intervention studies was performed in order to quantify the effects of periodontal treatment on HbA1c level among diabetic patients. Three investigators extracted data regarding intervention, outcomes, and effect size. A total of 456 patients were included in this analysis, with periodontal treatment as predictor and the actual change in hemoglobin A1c level as the outcome. The weighted average decrease in actual HbA1c level was 0.38% for all studies, 0.66% when restricted to type 2 diabetic patients, and 0.71% if antibiotics were given to them. However, none was statistically significant **(Janket et al. 2005).**

6.0 Diabetic patients in dental office

Diabetes mellitus affects people of all ages, and its prevalence has been increasing. Epidemiological studies show that half of the patients with type 2 diabetes are undiagnosed. Patients with undiagnosed diabetes may have several intraoral signs like multiple periodontal abscesses, exophytic tissue extending from periodontal pocket, mobile teeth and severe bone loss. If the dentist suspects that a patient has undiagnosed diabetes, the patient should be asked about the cardinal signs and symptoms of diabetes (***poydipsia*** "excessive thirst", ***polyurea*** "excessive urination", and ***polyphagia*** "excessive hunger, often with unexplained weight loss"). These patients should be referred to physician for consultation.

Patients with diagnosed diabetes will be identified by history. A thorough registration of their medical history is needed; including

- Type of diabetes (type 1, type 2), How long the patient have had diabetes?
- Type of medical treatment (oral hypoglycaemic agents, insulin, diet).
- Glycemic control. Fasting blood glucose and HbA_{1c} with regular medical updates.
- Systemic complications resulting from diabetes, (e.g., hypertension, cardiovascular disease, etc.). The dentist may consult the patient's physician to discuss modifications to the treatment plan, particularly when surgical procedures are anticipated.
- Acute complications, e.g., hypoglycaemic episodes, frequency and severity.

Dentists must educate patients and their physicians about the interrelationship between oral health and diabetes mellitus.

Morning appointments are advisable since endogenous cortisol levels are generally higher at this time (cortisol increases blood sugar levels); makes them more tolerable for stress initiated from dental treatment. It is important that the diabetic patients eat their breakfast and take their medications before the appointment. Stress reduction and adequate pain control also are important during and after dental treatment.

Any patient with diabetes who is going to receive extensive periodontal or oral surgery procedures should be given dietary instructions after surgery. It is important that the total caloric content of the diet remain the same so that proper glycemic control of the diabetes is maintained.

Patient's physician should also be consulted about dosage modifications of medications in case of longstanding treatment session. E.g. patients with type 1 can reduce insulin dose before appointment while patients with type-2 can reduce oral antihyperglycemic medications. This is important in order to reduce the risk of hypoglycaemia under the operation. **Hypoglycemia** is the most common diabetic complication encountered in the dental office. It is common in patients treated with insulin and some oral hypoglycemic agents like sulfonylurease. In fact all diabetic patients have the risk of developing hypoglycaemia associated with dental treatment because off stress, pain, and imbalance between dietary intake and medication. The most common cause is that patients take their normal medications and eliminate or reduce a meal before the appointment. It is advisable to instruct the diabetic patients to bring their glucometers to the dental office. Before treatment, patients can assess their blood glucose in a matter of seconds. If the blood glucose level is at or near the lower limits (about 70 - 90 mg/dl), they can be given carbohydrates orally to prevent peroperative hypoglycaemia.

Signs and symptoms of hypoglycaemia are most common when blood glucose levels decrease to less than 60 mg/dl. The first set of symptoms are called neuro-genic (or sympathetic) because they relate to the nervous system's response to hypoglycemia. Patients may experience any of the following: nervousness, sweating, intense hunger, trembling, weakness, palpitation and often have trouble speaking. When blood glucose levels decreased beyond 45 mg/dl range, the brain is not getting enough glucose. At this point, symptoms progress to confusion, drowsiness, behaviour changes, unconsciousness and seizure. http://www.medicinenet.com/hypoglycemia/page2.htm.

Treatment of a hypoglycemic event aims to elevate glucose levels to the point where signs and symptoms are resolved and glucose levels return to normal. If the dentist suspects that the patient is experiencing a hypoglycemic episode, the treatment should be stopped. Immediately administer 15–20 g of fast-acting oral carbohydrate such as glucose tablets or gel, sugar, candy, soft drinks or juice. If the patient is unable to swallow or looses consciousness, the dentist should seek medical assistance.The drug of choice is 1 mg glucagon because it can also be given intramuscularly or subcutaneously. Glucagon causes immediate release of stored glucose from the liver into the blood stream. Normally the patient should respond within 10 min. When the patient is conscious, carbohydrate should be given orally to avoid reoccurrence of hypoglycemia. If the patient is not responding to glucagon treatment, then intravenous glucose should be given **(Felleskatalogen 2007).**

Patients with sustained hyperglycemia may develope diabetic coma in the dental office but it is very rare. It may be difficult for the dentist to differentiate between hyper and hypoglycemic attacks. One should always suspect hypoglycemia and begin with oral carbohydrates.

(Vernillo 2003, Rees & Mealey 2004, Mealey et al. 2006)

Summary:

- Good medical history including medications, regimen and the degree of glycemic control for diabetic patients.
- Try to explain the relationship between DM and oral diseases and the adverse effect of poor glycemic control and smoking related to the complications of DM.
- Avoid hypoglycaemic attack during treatment session by giving short morning appointments and make sure that the patient has eaten breakfast.
- Carbohydrate source like sugar, juice, soda, etc. and glucagon injection should be available in the dental office when treating a diabetic patient.

Recommendations to diabetic patients:

- Good glycemic control.
- Good oral hygiene.
- Regular dental visits.
- Consult your dentist if you get any abnormal signs and symptoms e.g., bleeding from gingiva, tooth mobility, abscess, etc.
- It is recommended to follow smoke-cessation programs because of documented negative effect of smoking on diabetic complications.
- When using dentures, clean thoroughly and watch possible changes in your oral soft tissues.

7.0 Conclusion:

There is general agreement that there is a significant relationship between diabetes and periodontitis. Many studies have shown a high prevalence of periodontitis in diabetic patients. In addition a higher prevalence and more aggressive periodontitis are found in patients with poorly controlled diabetes. The duration of having diabetes is an important factor that affects the progression and severity of periodontitis.

Alterations in the host response in diabetics to existing periodontal pathogens may be primarily responsible for the more aggressive periodontal destruction observed in patients with diabetes. Diabetes is characterized by hyperglycemia, which affects the host response by several mechanisms: AGE accumulation, vascular alteration, changes in oral environment due to increased glucose concentration in GCF resulting in shifts of the microbial flora and altered cell function like PMNs, fibroblasts and monocytes. These changes may lead to prolonged inflammation and impaired wound healing.

Periodontitis may alter glycemic control and increase the risk of progression of diabetic complications and increase the mortality rate of diabetes. The mechanism behind this is the increasing levels of inflammatory mediator TNF-α which increase insulin resistance leading to poor glycemic control.

Treatment of diabetic patient is highly dependent on the degree of glycemic control. Well controlled diabetics can be treated as non-diabetics, but the risk of peroperative hypoglycaemia should be considered. Conventional periodontal therapy combined with antibiotics may enhance glycemic control in poorly controlled subjects.

Patients with previously undiagnosed type 2 diabetes may have several intraoral signs like multiple periodontal abscesses, exophytic tissue extending from periodontal pocket, mobile teeth and severe bone loss etc. The referral of these patients to the physician may help in early diagnosis.

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